Aus der Klinik für Audiologie und Phoniatrie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Influence of phonosurgical interventions and special vocal effects on glottal opening and closing function and phonation

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von
Ahmed Ibrahim Nasr
aus Zagazig/Sharkia (Ägypten)

Datum der Promotion: 23.06.2019

Inhaltsverzeichnis

List of Abbreviations

BVFP	bilateral vocal fold paralysis
CaHA	calcium hydroxylapatite
DiVAS	digital video archiving and evaluation system
DSI	dysphonia severity index
EGG	electroglottography
FEV1	forced expiratory volume at 1 second
FOIS	functional oral intake scale
FU	follow up
FVC	forced vital capacity
GRB	overall grade of hoarseness (G), roughness (R), breathiness (B) scale
LTAS	long-term average spectrum
MPT	maximum phonation time
n.s.	not significant
PAS	penetration aspiration scale
PEF	peak expiratory flow
PIF	peak inspiratory flow
RBH	roughness (R), breathiness (B), hoarseness (H) scale
SD	standard deviation
SPL	sound pressure level
VF	vocal fold
VHI	voice handicap index
VLS	videolaryngostroboscopy
VRP	voice range profile
VSK	videostrobokymography

Abstract

In this cumulative dissertation we examined the influence of phonosurgical interventions and special vocal effects on glottal opening and closing function and phonation. In a first prospective observational multicentre trial we investigated the phonosurgical effect of posterior chordotomy and partial arytenoidectomy on glottal function. The residual glottal gap causes dysphonia. Yet the resulting improvement of breathing is much more important. 61 patients with bilateral vocal fold paralysis (BVFP) were screened of whom 36 were eligible. Subjects underwent standardized phoniatric and respiratory tests preoperatively and at one and six months postoperatively. The respiratory parameters improved significantly. Voice quality objectively worsened significantly; however, this was not perceived by the patients themselves. We conclude that endoscopic glottal enlargement is an effective method for relieving symptoms of dyspnoea due to BVFP. In a second prospective clinical pilot study we evaluated the efficacy of vocal fold augmentation with calcium hydroxylapatite (CaHA) in surgically pretreated larynges with glottal insufficiency. After several prior reconstructive attempts, CaHA was injected in 10 patients with residual glottal insufficiency $\leq$ 1.5 mm. Results were assessed after one day, one and three months. Evaluation of augmentation comprised intraoperative documentation, videolaryngostroboscopy (VLS), and voice function diagnostics. The study revealed that in pretreated vocal folds the exact placement of CaHA was not possible. Due to the insufficient augmentation, the voices did not improve. We conclude that the application of CaHA in the surgically pretreated scarred larynx is not reliable to improve phonation. In a third individual cohort study we investigated common vocal effects in professional nonclassical vocalists. Ten male singers (pop, rock, metal, musical theatre) repeatedly presented the usual nonclassical vocal effects in their repertoire. All performances were documented and analysed. VLS showed that the vocal apparatus of all singers was healthy. The vocal effects could be easily differentiated from each other; they were intraindividually consistently repeatable and also interindividually produced in a similar way. Partial glottal vibration was discovered in one singer when belting in the high register. We conclude that the long-lasting use of nonclassical effects does not necessarily cause negative impact on trained singers. The risk of long-term vocal fold damage depends on the individual constitution, duration, and extent of the hyperfunction. In summary, the investigated vocal effects and phonosurgical interventions had an important influence on glottal function and phonation, while in laryngeal diseases the treatment outcomes for respiration and voice might behave contrary to each other.

Zusammenfassung

In dieser kumulativen Dissertation wurde der Einfluss phonochirurgischer Interventionen und spezieller Stimmeffekte auf die glottale Öffnungs- und Schließfunktion sowie auf die Phonation untersucht. In einer ersten, prospektiv-multizentrischen Studie wurde der Effekt der posterioren Chordotomie und der partiellen Arytenoidektomie auf die Stimmlippenebene untersucht. Der vergrößerte Glottisspalt verursacht Dysphonie, wobei die resultierende Verbesserung der Atemfunktion im Vordergrund steht. Von 61 Patienten mit bilateraler Stimmlippenlähmung (BVFP) wurden 36 in die Studie eingeschlossen. Die Probanden unterzogen sich prä- sowie 1 und 6 Monate postoperativ einer standardisierten Atem- und Stimmfunktionsdiagnostik. Die Atemfunktion verbesserte sich postinterventionell signifikant. Die Stimmqualität verschlechterte sich objektiv, was von den Patienten jedoch subjektiv nicht wahrgenommen wurde. Wir schlussfolgern, dass die endoskopische Glottiserweiterung eine effektive Methode zur Besserung der Dyspnoe bei BVFP ist. In einer zweiten, prospektiv-klinischen Pilotstudie wurde die Wirksamkeit der Stimmlippenaugmentation mit Calciumhydroxylapatit (CaHA) bei operativ vorbehandelten Patienten mit Glottisschlussinsuffizienz untersucht. Nach mehreren vorangegangenen rekonstruktiven Eingriffen wurde CaHA bei 10 Patienten mit einer Rest-Glottisschlussinsuffizienz $\leq$ 1,5 mm injiziert. Die Ergebnisse wurden nach einem Tag, sowie nach 1 und 3 Monaten bewertet. Die Evaluierung der Augmentation umfasste die intraoperative Dokumentation, Videolaryngostroboskopie (VLS) und Stimmfunktionsdiagnostik. Die Studie zeigte, dass eine exakte Platzierung von CaHA in die vorbehandelten Stimmlippen nicht möglich war. Aufgrund der unzureichenden Augmentation verbesserten sich die Stimmen nicht. Wir schließen daraus, dass die CaHA-Applikation in chirurgisch vorbehandelten, vernarbten Kehlköpfen die Phonation nicht verlässlich bessert. In einer dritten, prospektiv-klinischen Kohortenstudie untersuchten wir gängige Stimmeffekte bei professionellen nicht-klassischen Vokalisten. Zehn männliche Sänger (Pop, Rock, Metal, Musical) präsentierten wiederholt die die in ihrem Repertoire üblichen nicht-klassischen Stimmeffekte. Alle Darbietungen wurden dokumentiert und analysiert. Die VLS zeigte, dass der Stimmapparat aller Sänger gesund war. Alle Effekte ließen sich auditiv gut voneinander differenzieren. Sie waren intraindividuell sicher gleichartig reproduzierbar und wurden auch interindividuell weitestgehend konsistent gebildet. Bei einem Sänger wurden beim Belten im hohen Register partielle Stimmlippenvibrationen entdeckt. Wir schlussfolgern, dass bei ausgebildeten Sängern die untersuchten nicht-klassischen Stimmeffekte per se nicht zu direkten negativen Beeinträchtigungen führen. Das längerfristige Risiko einer stimmlippenschädigenden Wirkung hängt von der individuellen Konstitution, der

Dauer und vom Ausmaß der Hyperfunktion ab. Zusammenfassend zeigten die untersuchten Stimmeffekte und phonochirurgischen Eingriffe einen bedeutenden Einfluss auf Glottisfunktion und Phonation, wobei sich die Auswirkungen für Atmung und Stimme einander entgegengesetzt darstellen können.

1. Introduction

Normal Glottal function is critical for both phonation and respiration. The presence of impaired glottal opening leads to hoarseness of voice and respiratory difficulties up to stridor. The presence of impaired closure (glottal gap) leads to vocal hoarseness of different degrees. Also, swallowing function of the larynx is mostly affected. Humans can intentionally or unintentionally compensate the presence of insufficient glottal closure using supraglottal structures. Even without the presence of glottal gap (insufficient closure) some people are able to set their supralaryngeal structures in action during phonation. The produced voice is of course different from the normally produced glottal voice via the vocal folds (VF), yet it is mostly sufficient for communication.

Glottal gaps can be either physiological or pathological. The latter are multifactorial, predominantly organic in origin and occasionally functional. Organic causes include VF paralysis or scarring, as well as a deficiency or excess of tissue. In addition to loss of the mucosal wave, the degree of hoarseness is primarily determined by the circumferential area of the glottal gap. It is thus important to quantify the extent of glottal insufficiency. Although the patient's symptoms form the basis for treatment decisions, these may be subjective and inadequately reflected by the results of auditory-perceptual evaluation, voice analysis and voice performance tests.

Impaired glottal opening is mostly due to VF paralysis. The most common cause is iatrogenic paralysis for example after thyroid surgery. Unilateral VF paralysis may cause respiratory problems. If both VF are paralyzed and lying at the middle line, the patient will have a life threatening stridor.

The aim of this cumulative dissertation was to investigate the influence of phonosurgical interventions and special vocal effects on glottal function and phonation. In our first study we planned to examine patients suffering from impaired glottal opening due to bilateral vocal fold paralysis (BFVP). Patients were treated by phonosurgical interventions for glottal enlargement. As a result, glottal function and phonation are affected. The residual glottal gap causes dysphonia and in some cases swallowing problems like aspiration of fluids. Yet the resulting improvement of breathing is much more important than the voice deterioration. To quantify the outcome and to understand the effect of such operative technique on patients' voice, swallowing and breathing function, we examined these patients before and after the surgical intervention in a multicentre study.

In our second study we planned to examine subjects with dysphonia who underwent several prior reconstructive attempts to treat glottal gaps following tumor resection, VF paralysis, in sulcus vocalis, and VF scarring. We tried to improve the glottal closure either on glottal or supraglottal levels performing injection laryngoplasty. Radiesse Voice, a synthetic calcium hydroxylapatite (CaHA), was injected under general anaesthesia using a transoral microlaryngoscopic approach. Short- and long-term evaluation of augmentation comprised intraoperative video- and photo-documentation, pre-and postoperative videolaryngostroboscopy (VLS), as well as established subjective and objective voice function diagnostics.

In our last study we planned to examine the intentionally induced laryngeal closure at supraglottal level. This sort of closure can be achieved using special vocal effects during non-classical singing. Experienced professional non-classical singers with different stylistic backgrounds (pop, rock, metal, musical theatre) were examined. Participants repeatedly presented the usual non-classical vocal effects and techniques in their repertoire. All performances were documented and analyzed using established instruments (e.g., auditory-perceptual assessment, VLS, electroglottography (EGG), and voice function diagnostics). The vocal effects were multidimensionally investigated, to examine their mechanism of production and reproducibility, to validate the existence of partial glottal vibration, and to assess the potential of damage to the voice from non-classical singing.

2. Material and Methods

2.1 Voice and respiratory outcomes after permanent transoral surgery of BVFP

This prospective, multicentre, observational study was performed from October 2010 until June 2014. From altogether 61 patients who were screened for inclusion, 36 subjects were involved, and 32 of them completed the study (2 drop outs, 2 withdrawals). Patients aged between 18 and 75 years with BVFP diagnosis and indication for enlargement surgery were recruited. Subjects needing revision surgery were included if the previous intervention was not permanent (e.g., temporary laterofixation) and did not result in benefit. Surgical procedures were comprised of posterior chordotomy, partial or total arytenoidectomy, permanent laterofixation, or combinations of these techniques. The appropriate method was selected according to the experience of the surgeon and the specific needs of the patient. All surgery was performed under general anaesthesia via microlaryngoscopy.

For evaluation of respiration, spirometry was performed by experienced medical personnel

according to the guidelines of the German Society for Pneumology and Respiratory Medicine. Postoperatively, patients were asked to record the peak expiratory flow (PEF) weekly by self-measurement with a PEF meter (asma-1; Vitalograph, Ennis, Ireland). The swallowing capability of the subjects was evaluated by means of the Functional Oral Intake Scale (FOIS) and the Penetration-Aspiration Scale (PAS). Concerning phoniatric aspects, VLS were performed preoperatively and at the 6-months postoperative visits. The description of VF vibration was restricted to the aspects of mucosal wave propagation, the closed phase, and nonvibrating parts. Mucosal wave propagation was graded as 0 = normal, 1 = impaired, 2 = severely impaired, or 3 = not detectable. Voice recordings were stored in *.wav format on a hard disc, with a sampling rate of 22 Hz for later analysis. Norm values and procedures were based on European Laryngological Society guidelines. Acoustic analysis was conducted using the most stable part of the phonation and comprises maximum phonation time (MPT) and voice range profile (VRP). Vocal range was evaluated in semitones in order to avoid gender-specific bias. For perceptive voice analysis, the RBH scheme was used to evaluate the severity of roughness (R), breathiness (B), and hoarseness (H) on a scale from 0 to 3 (0 = no deviance, 1 = mild deviance, 2 = moderate deviance, and 3 = severe deviance). Mean values of a group of five raters were taken. The Dysphonia Severity Index (DSI) was used as an established objective and quantitative measure of voice quality. Sound pressure level (SPL) analysis was applied as an indicator of VF vibration intensity. An abbreviated form of the Voice Handicap Index (VHI), the VHI-12, was used for the self-assessment of voice.

Statistical analysis was performed with IBM SPSS 21 statistics software (IBM Corp., Armonk, NY). Metric variables were tested for normal distribution by Kolmogorov-Smirnov test. Analysis of variance with repeated measurements was applied for comparison of mean values at different time points. Wilcoxon-signed rank test was used for nonparametric calculation in variables other than metric. Pearson correlation was used for metric variables, whereas Spearman-Rho correlation was used for categorical variables. All P values were results of two-sided tests; level of significance was set at $P<0.05$.

2.2 Use of injectable CaHA in the surgically pretreated larynx with glottal insufficiency

CaHA was injected under general anaesthesia using a transoral microlaryngoscopic approach in patients with residual glottal insufficiency ≤ 1.5 mm. Selection criteria were unsatisfactory result after preceding phonosurgery, tumor-free interval of at least 5 years, and inefficient long-term voice training. The initial study protocol was designed to investigate 30 patients with interim analyses after 10 and 20 patients (adaptive design). Due to the limited success of the CaHA

injection procedure described in this study and the presence of more efficient augmentation techniques, we decided to end the study prematurely after including 10 patients (6 male, 4 female), aged between 30 and 76 years (54±14 years [mean±SD]).

According to the manufacturer's instructions, CaHA injection was performed with an overcorrection of about 10% to 15%; otherwise, the whole amount in the syringe (1 mL) was injected. Previous implants (adipose tissue after fat augmentation) and relocated structures (cartilage after medialization thyroplasty) were left in place. The particular injection sites depended on the shape and size of the glottal defect. The injected structures were located at the level of the pretreated VFs on either one or both sides. The aim of the augmentation was to fill the residual defect and to improve the glottal closure, resulting in vibration of potentially voice-producing structures. Intraoperative video and photo documentation was done to allow detailed observation of the injection procedure and the augmentation effect. The uniform postoperative assessment was planned after 1 day, and 1 and 3 months.

Pre- and postoperative data were collected by means of objective und subjective methods. Digital VLS was carried out using a high-resolution rigid videolaryngoscope with integrated microphone connected to the Endo-STROB control unit (XION Medical, Berlin, Germany). Auditory-perceptual voice evaluation was independently assessed by three experienced phonosurgeons using the GRB system, to judge the overall grade of hoarseness (G), roughness (R), and breathiness (B). The nine-item VHI-9i questionnaire was used for the patients to provide self-assessment of their own voice. VRP and acoustic–aerodynamic analysis were performed to obtain objective quantitative measurements of speaking and singing voice. These recordings were conducted preoperatively and 3 months postoperatively by an experienced technician using the DiVAS software, without knowing the exact treatment status (pre- or postoperative). The results were assessed statistically with SPSS 20 using descriptive findings, mean Wilcoxon signed rank test for related samples, and mean Spearman rank correlation coefficient. Significance was set at $P<0.05$. Fleiss' kappa was used for assessing the reliability of agreement between all three raters when assigning categorical GRB ratings to the patient's voices.

2.3 Common vocal effects and partial glottal vibration in professional nonclassical singers

Altogether, 10 male singers aged between 25 and 46 years (34±7 years [mean±SD]) with different stylistic backgrounds were recruited. Their time of professional engagement amounted to between 2 and 23 years (10±7 years). Participants were musical theater singers (n=5) and pop/ rock/ metal singers (n=5). The selection criteria were normal laryngeal anatomy, absence of dysphonia, and informed consent.

All presented vocalizations had to be applied regularly in the everyday life of the singer, meaning they were practiced and subjectively reproducible. The order of presentation was oriented on the source of vocalization beginning at the glottal level and extending to supraglottal effects. The easier and less powerful exercises came first. The participants were allowed to start directly with the specific effect or to modulate a straight tone (sequence: straight tone, effect, straight tone). Every effect had to be produced three times on vocalises and text excerpts, at a self-chosen pitch. In addition, the musical theater singers were asked to present Papageno's Bird-Catcher aria from Mozart's "The Magic Flute" using belt, twang, and bel canto style. This was done for comparison of the spectral characteristics of different voice qualities because all of the musical theater singers were trained in these three styles of singing. Two experienced singing teachers confirmed the typical sound and type of production of the presented effects and singing styles by auditory perception.

The performances and singing effects were documented by means of established objective diagnostic instruments such as transnasal VLS, videostrobokymography (VSK), transcutaneous EGG, and acoustic-aerodynamic voice function diagnostics. The VLS, EEG recordings, and acoustic measurements were done simultaneously during the singing tasks using the multimodal XION system. VLS was carried out applying the flexible, high-resolution chip-on-the-tip video nasopharyngoscope EV-NE (3.4 mm tube diameter). Being equipped with a combined camera, light, optics, and microphone, this device was connected to the Endo-STROB control unit. The DiVAS software was used for automatic recording, archiving, and analysis of all video and audio sequences, images, and measurement data. Auditory-perceptual voice evaluation was assessed by using the RBH system. Audio samples served for a subjective classification of the vocal effects. The recordings were shuffled and blinded regarding patient assignment and effect. Five experienced listeners (3 phoniatricians, 2 singing teachers) independently rated all audio files in one session. Consensus concerning the type of presented effects and singing styles was required to use the audio recordings for further evaluation. Three senior phoniatricians with expertise in VLS, VSK, EGG, and acoustic-aerodynamic evaluation analyzed the objective measurements.

3. Results

3.1 Voice and respiratory outcomes after permanent transoral surgery of BVFP

The respiratory improvements observed in PEF ($P<0.001$) were significant when the status 6 months postoperatively was compared with the preoperative baseline. Self-measurement with the

PEF meter revealed significant improvement in respiration from baseline to 1 month (P=0.008) and 6 months (P=0.002) postoperatively. The analysis of the PEF-meter values correlated significantly with the spirometry results at 6 months postoperatively (PEF in L/min; Pearson correlation: r=0.842; P<0.001).

Preoperative swallowing status investigated with FOIS and PAS score was normal in most patients. At 6 months postoperative, one of 32 subjects experienced a deterioration which was not attributable to the glottal enlargement procedure.

The VLS revealed that the glottal gap during respiration increased significantly from a median preoperative width of 2.5 mm to 4.6 mm, 6 months postoperatively (P<0.001). The remaining portion of the VF on the operated side was significantly reduced (P<0.001) from the whole length of 4/4 (100%) to 2.5/4 (62.5%); i.e., on average 2/3 of the VF was preserved. The analysis of the maximal abduction showed a significant shift from the median position (pre) to the intermediate position (6 months post). Analysis of the mucosal wave showed a decrease in the number of normal cases (from 21% to 0%) and an increase of the cases where no mucosal wave could be detected (from 26.3% to 47.4%) when the condition at 6 months postoperatively was compared with the preoperative situation. The decrease showed a trend toward significance (P=0.06). The closed phase was either short or not detectable.

Maximum phonation time, as a test of vocal function and glottal competence, showed a significant decrease between the preoperative status and 1 month (P=0.01) and 6 months (P=0.014) postoperatively. Results did not differ between 1 month and 6 months postoperatively (P=0.7). Values of the vocal range in semitones decreased significantly from the preoperative to the 1 month postoperative visit (P=0.02), and from the preoperative to the 6 months postoperative visit (P=0.002). Dynamic range did not change significantly over the observed period. Jitter analysis was above the normal range, indicating pathological values throughout the entire period. DSI values exposed moderate voice impairment. Rating of vocal quality in terms of the RBH scale revealed a significant increase of breathiness and hoarseness from the preoperative status compared to the situation 1 and 6 months postoperatively (P<0.01) and no changes of roughness over time (P>0.5). The VHI-12 did not change significantly either when the preoperative situation was compared with the 1-month postoperative condition (P=0.66) or with the 6-month postoperative condition (P=0.14). The mean value indicated moderate voice impairment at all time points.

3.2 Use of injectable CaHA in the surgically pretreated larynx with glottal insufficiency

During the microlaryngoscopic augmentation procedure it became apparent that an exact

placement of Radiesse Voice was not possible in the pretreated VF with no or minimal lamina propria remaining. We observed in these patients unpredictable CaHA propagation into the scarred tissue. In 80% of the patients the injected material came partly back out from the puncture channel when the injection needle was retracted. Furthermore, CaHA squirted out of ruptured tissue sites during augmentation in 50% of the patients. The amount of successfully injected material differed from 0.5 to 1.0 mL (0.8±0.2).

Within the follow-up (FU) period (106±74 days; median 84 days) we observed an intermittent local swelling and redness with no relevant side effects. Dysphagia was not observed. However, the long-term results showed in general insufficient postoperative augmentation compared to the preoperative situation. The VLS assessment after 1 day revealed localized swelling with complete glottal closure in 80% of the patients. After 1 and 3 months the swelling decreased, and the glottal insufficiencies increased gradually to the degree of the preoperative findings. Objective data about voice function and VRP showed no statistically significant change. The vocal quality in terms of auditory perceptual assessment using the GRB system did not change either. In 90% of the patients, RGB still ranged from moderate to high (preoperative 2.5±0.7 vs. postoperative 2.3±1.1). The inter-rater reliability indicated substantial agreement between the ratings of all three phonosurgeons (□κ=0.72). Comparison of all voices based on overall grade showed a slight postoperative improvement of voice quality in 7/10, and slight deterioration of voice in 3/10 patients. Due to the small sample size, these changes were shown to be statistically insignificant according to the Wilcoxon signed rank test (P =0.72).

Considering the speaking voice profile, a significant increase of the vocal range from 6.2±3.2 to 8.7±3.9 semitones was observed (P=0.02). All other acoustic and aerodynamic parameters remained mostly unchanged; the marginal differences between pre- and postoperative findings were not significant (n.s.). The VHI-9i fell from an average of 22±10 to 19±10 points (n.s.), indicating a moderate voice disorder. The intraindividual comparison showed in 7/10 patients a postoperative improvement, and in 3/10 patients the intraindividual comparison showed a deterioration (P=0.17). The correlation of these intraindividual changes with those of the auditory evaluation was not significant (r_s=–0.50; P=0.14). Also in the VHIs, the overall self-perceived impairment of voice remained moderately disturbed.

3.3 Common vocal effects and partial glottal vibration in professional nonclassical singers

All singers had healthy voices without any hoarseness (R0B0H0). In their past medical history, there was no evidence of suffering from relevant periods of dysphonia or dysodia. The anamnestic use of the vocal effects which were intended to be investigated amounted to between

8 and 27 years (12±6 years [mean±SD]). All singers showed normal laryngeal anatomy in the VLS examination. However, the quantity of mucus moistening in the larynx was enhanced in 7 of 10 singers. The increased mucus production was used partially as an additional vibrating element with a stylistically desired effect of adding impurity to the voice quality.

In summary, the following nonclassical vocal effects were produced: Breathy, Creaky, Vocal fry, Grunting, Rattle, Growling, Distortion, Belting, and Twang. VLS demonstrated, where these effects were generated: at glottal level (e.g., Breathy, Creaky, Vocal fry, Grunting) or at supraglottal level (e.g., Rattle, Distortion). VSK resulted in one-dimensional images of stacked lines over time indicating the horizontal wave movement of the VFs during phonation. This diagnostic procedure revealed important information about the glottal closure, the regularity and symmetry of the mucosal wave propagation. The EGG diagram showed characteristic waveforms and allowed evaluation of the oscillation cycles including amplitudes and phases (closing, closed, opening, open phase). All effects were intraindividually consistently repeatable and also interindividually reproducible with high consistency. They could be easily differentiated from each other by auditory-perceptual voice evaluation.

The presentation of Papageno's Bird-Catcher aria from Mozart's "The Magic Flute" showed significant differences between belt, twang, and classical bel canto singing techniques. Belt was characterized by a spectral tilt in the long-term average spectrum (LTAS) without formation of the singer's formant clusters. The tone quality was more direct. In addition to a higher laryngeal position, the settings in the vocal tract and face were different (e.g., showing teeth, higher tongue, broader mouth opening, assumed tense velum, contraction of the procerus muscle). In twang, due to the specific shaping of supralaryngeal and pharyngeal structures, the LTAS showed a strong concentration of acoustic energy between 3 and 5.5 kHz. This created a special timbre with the impression of a quacking, metallic-nasal sound, whereby the speech quality was very present. In the classical vocal technique (bel canto), the resonance clustering in the LTAS was around 3 kHz. In addition to this singer's formant cluster, which constitutes the projection and ring of the classical singing voice, a deeper position of the larynx, a pronounced resonance strategy, and a balanced timbre in all parts of the range were found.

A special feature in one singer was reproducible partial glottal vibration when belting in the high register. He habitually pressed the closed posterior part of the glottis together, and both VF showed phonatory movement only in their anterior portion. The sonagram displayed attenuated harmonics. Auditory perceptual assessment revealed a loss of volume, which was confirmed by reduced values for mean SPL recorded during VLS. The sound impression was hollower, disembodied, and slightly dampened. The unwanted transition to this reduced voice quality was

accompanied by physical fatigue and inflexible respiratory support.

4. Discussion

The investigated vocal effects and phonosurgical interventions had an important influence on glottal opening and closing function and phonation.

According to the literature, our first study is so far the biggest prospective trial investigating respiratory and phoniatric outcomes in BVFP patients. Only a few studies examined the effects of glottal enlargement on spirometry outcomes according to international guidelines [1]. In BVFP patients, it is assumed that the narrow glottal gap impairs upper airway function, and consequently has an impact on the functional parameters of the lower airway. Only a handful of prospective studies in this field have included a significant amount of cases [2-7]. This might explain the surprising finding that in a large series of total arytenoidectomies, which is a fairly extended intervention, aerodynamic parameters worsened, whereas postoperative breathing ability increased [4]. The same study reported subjective worsening of the voice in 94% of all cases. Another long-term study (1 year FU) investigated the effects of posterior transverse laser chordotomy in 22 patients, of whom six were tracheotomized prior to treatment [6]. FEV1, FEV1/FVC, and PEF values increased considerably. Significant disturbances of jitter, shimmer, fundamental frequency, and harmonics-to-noise ratio observed directly after the surgical intervention improved at 1 year FU. For the majority of the patients, respiratory quality was considered more important than voice quality. According to our results, endoscopic glottal enlargement is an effective method for relieving symptoms of dyspnea due to BVFP, although values were still in the pathological range. Whereas key spirometry parameters increased postoperatively (PEF, PIF), objectively assessed voice parameters indicate an impaired function. However, these are not necessarily perceived as such by the patients (VHI-12); relief of dyspnea appears to compensate for the decreased voice quality. No detrimental effects on swallowing could be identified. However, long-term results cannot be predicted. A study by Misiolek et al. showed long-term results deterioration, but this did not match with the patients' subjective impression [1]. Regarding VLS findings, the resection in the region of the VF led to a wider glottal gap, reduced closure during phonation, scarring, and the extension of the nonvibrating portion at the expense of the vibrating part. The obtained measurements suggest an apparent degree of accuracy, but this should be considered with caution, even if the tendency of an increased glottal width after surgery is supported by this rough estimation. Six months

postoperatively, we observed increased glottal gap correlating significantly with improved PEF and PIF. In terms of general opening of the glottis, the treated VF moved significantly to a more abducted position from the preoperative to the 6 month postoperative situation, but this did not correlate with PIF, PEF, or with any other subjective or objective voice parameter. Interestingly, there was a significant correlation of PIF with the remaining adduction mobility of the side that was not operated. This fact allows the prediction of better respiratory results for those patients who do not have not completely immobile VFs. One would expect that the grade of abduction correlates with PIF values. Our interpretation of the puzzling result is that a tense VF imposes less resistance to the inspiratory airflow than a flaccid one. In contrast to this, we were able to see a significant correlation of the voice range and the maximum SPL with adduction pre- but not 6 months postoperatively. This result suggests that the extent of functional loss due to the expected damage of the phonatory system caused by surgery could not be easily predicted by the findings before treatment; that is, good voices before surgery will not necessarily be good voices after surgery and vice versa. In general, VLS findings did not correlate strongly with voice and respiratory outcomes. The most predictive parameters seem to be the glottal gap for respiration and the remaining adduction of the untouched VF for the voice.

Concerning the results of our second study, the use of CaHA in the multiple pretreated larynx did not prove to be a good option to achieve a sufficient glottal closure and thereby a satisfactory improvement of voice. In the majority of patients, the vocal sound improved only by nuances that cannot be differentiated by the ordinal classification of the GRB system. However, the vocal range of the speaking voice enlarged significantly, supporting the overall impression of many patients that speaking becomes easier after the injection. The reduction of strain during speaking, which is in line with the slightly improved MPT, is a known benefit after VF augmentation as stated in other injection Laryngoplasty studies [8,9]. The exact placement of Radiesse Voice in the scar tissue of pretreated VFs with no or minimal lamina propria remaining was not possible. There may be unpredictable CaHA propagation along tissue spaces and connective tissue based scar tracks. If the capacity of the laryngeal structures to be augmented is exceeded, the injected material comes back out from the puncture channels when the injection needle is retracted. Once the pressure during injection breaks the tissue resistance, CaHA might even squirt out of ruptured tissue sites (locus minoris resistentiae). The absorption capacity seems to depend on the severity of scar formation of the pretreated tissue [10]. Increasing numbers of preceding surgical interventions with subsequent scar formation and stiffness of the tissue resulted in more unpredictable CaHA injection treatment with less augmentation success. According to our experience, the standard amount of 1 mL of Radiesse Voice is not always sufficient to achieve

glottal closure, thus facilitating tissue vibration in the pretreated scarred larynx. In cases when a larger amount is needed, the augmentation with autologous periumbilical fat is a more suitable alternative [11]. This procedure is also preferable due to the nonexistent cost factor of the injected substance and the simplicity of acquiring a sufficient quantity of material needed for the augmentation. However, up to now, no injection material exists that can restore the lamina propria or replace the ideal viscoelasticity of normal VFs. Another relevant problem is the absorption of these materials over time. In contrast to the presented effects, CaHA yields satisfactory results in medialization of the unaltered VF (e.g., in VF paresis) [10,12,13]. Also, in the patients in our study with a pretreated scarred hemilarynx, injection of the nonaffected VF will result in projection of that side. Therefore, we recommend this procedure as a subsequent therapy in cases where the pretreated VF with no or minimal lamina propria remaining will not accept any material and has a quite straight free VF margin. Injecting the nonoperated soft side can improve the glottal closure, resulting in vibration of potentially voice producing structures. In these cases the best outcomes are reached when the substance is placed deep in the thyroarytenoid muscle. The deposition of CaHA in the lamina propria under the epithelium affects vocal quality negatively [14]. Caution is also necessary in patients with a history of laryngeal malignancy, because injection sites can enhance on positron emission tomography scans, which are used in oncological post-treatment monitoring [15]. Therefore, we chose CaHA as an injection material only in patients with cancer FU > 5 years without signs of recurrence. Though CaHA is a welcome addition to our armamentarium against glottal insufficiency, the suitability for augmentation of scar tissue in the larynx must be considered carefully in each individual case.

The systematization of the results of our third study reveals that nonclassical singing effects are principally caused by two mechanisms: (1) oscillation changes of the larynx (influencing the tone generation on glottal or supraglottal level), and (2) configuration changes of the vocal tract (influencing the tone by height of the larynx and the variation of resonances). It is the first study which demonstrates the existence of partial glottal vibration as a possible reason for the loss of loudness in male singers when belting in the high register. Compared with the classical bel canto sound, other singing techniques and the production of most nonclassical vocal effects were confirmed to be accompanied by LTAS changes [16-18] and a subjectively higher pressure, which was both visible and audible during singing. However, the larger forces acting on the laryngeal mucosa and in particular the VFs did not lead to obvious signs of mechanical damage in the investigated singers. The accurate analysis, understanding, and pedagogical teaching of these techniques, including how to correctly produce the described nonclassical vocal effects, are

of great importance to keep a healthy voice [19-21]. Without this knowledge and training by experienced singing teachers, there is a high risk of damaging important laryngeal structures, which can manifest itself in acute injuries or in secondary acquired lesions due to chronic overload (eg, VF nodules) [22,23]. The possibility of long-term negative consequences depends on the individual constitution, specific use, duration, and extent of the hyperfunction [24]. The dangers can also be minimized if the vocalists intermittently take short relaxation breaks during hyperfunctional vocalization in order to recover and not to overstrain their voice [25]. In particular, if these effects are used only briefly, controlled, rather carefully, and as a specific means of expression, voice damage is not to be feared. However, some singers produce phonation with high SPL in order to compensate for a deficit of resonance in the vocal tract. Others sing with medium intensity and use the technical possibilities of the microphone and amplifiers while on stage. If the microphone is covered with the hands, in addition to feedback and distortion phenomena, targeted cupping effects can be generated that compress certain frequencies and make the vocal effects louder and denser. The effect of microphone type and placement on acoustic measurements and voice amplification is technically investigated in research and practically experienced while on stage [26-28]. Therefore, in addition to a properly learned vocal technique - which includes the correct handling of glottis and supraglottis, airflow, diaphragmatic support, and vocal tract - sufficient knowledge about the microphone and the sound system such as directional characteristics and microphone selection are also helpful in maintaining a healthy voice. The incidence and consequences of partial glottal vibration require continuing investigation to learn more about efficient and healthy vocal function in nonclassical singing.

5. References

1. Misiolek M, Ziora D, Namyslowski G, Misiolek H, Kucia J, Scierski W, Kozielski J, Warmuzinski K. Long-term results in patients after combined laser total arytenoidectomy with posterior cordectomy for bilateral vocal cord paralysis. Eur Arch Otorhinolaryngol 2007; 264:895–900.
2. Yilmaz T, Suslu N, Atay G, Ozer S, Gunaydin RO, Bajin MD. Comparison of voice and swallowing parameters after endoscopic total and partial arytenoidectomy for bilateral abductor vocal fold paralysis: a randomized trial. JAMA Otolaryngol Head Neck Surg 2013; 139:712–718.
3. Gorphe P, Hartl D, Primov-Fever A, Hans S, Crevier-Buchman L, Brasnu D. Endoscopic laser medial arytenoidectomy for treatment of bilateral vocal fold paralysis. Eur Arch Otorhinolaryngol 2013; 270:1701–1705.
4. Yilmaz T. Endoscopic total arytenoidectomy for bilateral abductor vocal fold paralysis: a new flap technique and personal experience with 50 cases. Laryngoscope 2012; 122:2219–2226.
5. Eckel HE, Thumfart M, Wassermann K, Vossing M, Thumfart WF. Cordectomy versus arytenoidectomy in the management of bilateral vocal cord paralysis. Ann Otol Rhinol Laryngol 1994; 103:852–857.
6. Dursun G, Gokcan MK. Aerodynamic, acoustic and functional results of posterior transverse laser cordotomy for bilateral abductor vocal fold paralysis. J Laryngol Otol 2006; 120:282–288.
7. Li Y, Pearce EC, Mainthia R, Athavale SM, Dang J, Ashmead DH, Garrett CG, Rousseau B, Billante CR, Zealear DL. Comparison of ventilation and voice outcomes between unilateral laryngeal pacing and unilateral cordotomy for the treatment of bilateral vocal fold paralysis. ORL J Otorhinolaryngol Relat Spec 2013; 75:68–73.
8. Sulica L, Rosen CA, Postma GN, Simpson B, Amin M, Courey M, Merati A. Current practice in injection augmentation of the vocal folds: indications, treatment principles, techniques, and complications. Laryngoscope 2010; 120:319–325.
9. Sardesai MG, Merati AL, Hu A, Birkent H. Impact of patient-related factors on the outcomes of office-based injection laryngoplasty. Laryngoscope 2016; 126:1806–1809.
10. Gillespie MB, Dozier TS, Day TA, Martin-Harris B, Nguyen SA. Effectiveness of calcium hydroxylapatite paste in vocal rehabilitation. Ann Otol Rhinol Laryngol 2009; 118:546–551.
11. Benninger MS, Hanick AL, Nowacki AS. Augmentation autologous adipose injections in the larynx. Ann Otol Rhinol Laryngol 2016; 125:25–30.
12. Carroll TL, Rosen CA. Long-term results of calcium hydroxylapatite for vocal fold augmentation. Laryngoscope 2011; 121:313–319.
13. Mohammed H, Masterson L, Gendy S, Nassif R. Outpatient based injection laryngoplasty for the management of unilateral vocal fold paralysis - clinical outcomes from a UK centre. Clin Otolaryngol 2016; 41:341–346.

14. Chheda NN, Rosen CA, Belafsky PC, Simpson CB, Postma GN. Revision laryngeal surgery for the suboptimal injection of calcium hydroxylapatite. Laryngoscope 2008; 118:2260–2263.
15. Grant N, Sulica L, DeCorato D. Calcium hydroxylapatite vocal fold injectable enhances on positron emission tomography. Otolaryngol Head Neck Surg 2008; 138:807–808.
16. Guzman M, Lanas A, Olavarria C, Azocar MJ, Muñoz D, Madrid S, Monsalve S, Martinez F, Vargas S, Cortez P, Mayerhoff RM. Laryngoscopic and spectral analysis of laryngeal and pharyngeal configuration in non-classical singing styles. J Voice 2015; 29:130.e21–e28.
17. McGlashan J, Thuesen MA, Sadolin C. Overdrive and Edge as Refiners of "Belting"?: An Empirical Study Qualifying and Categorizing "Belting" Based on Audio Perception, Laryngostroboscopic Imaging, Acoustics, LTAS, and EGG. J Voice 2017; 31:385.e11–385.e22.
18. Johnson AM, Kempster GB. Classification of the classical male singing voice using long-term average spectrum. J Voice 2011; 25:538–543.
19. Estill J. Belting and classic voice quality: some physiological differences. Med Probl Perform Art 1988; 3:37–43.
20. Yanagisawa E, Estill J, Kmucha ST, Leder SB. The contribution of aryepiglottic constriction to “ringing” voice quality - A videolaryngoscopic study with acoustic analysis. J Voice 1989; 3:342–350.
21. Gill BP, Herbst CT. Voice pedagogy - what do we need? Logoped Phoniatr Vocol 2016; 41:168–173.
22. Bourne T, Kenny D. Vocal qualities in music theater voice: perceptions of expert pedagogues. J Voice 2016; 30:128.e1–e12.
23. Beeman SA. Perceptions of voice teachers regarding students’ vocal behaviors during singing and speaking. J Voice 2017; 31:111.e19–111.e28.
24. D’haeseleer E, Claeys S, Meerschman I, Bettens K, Degeest S, Dijckmans C, De Smet J, Luyten A, Van Lierde K. Vocal characteristics and laryngoscopic findings in future musical theater performers. J Voice 2017; 31:462–469.
25. Haben CM. Voice rest and phonotrauma in singers. Med Probl Perform Art 2012; 27:165–168.
26. Titze IR, Winholtz WS. Effect of microphone type and placement on voice perturbation measurements. J Speech Hear Res 1993; 36:1177–1190.
27. Svec JG, Granqvist S. Guidelines for selecting microphones for human voice production research. Am J Speech Lang Pathol 2010; 19:356–368.
28. Zuckerwar AJ, Kuhn TR, Serbyn RM. Background noise in piezoresistive, electret condenser, and ceramic microphones. J Acoust Soc Am 2003; 113:3179–3187.

Eidesstattliche Versicherung

„Ich, Ahmed Ibrahim Nasr, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Influence of phonosurgical interventions and special vocal effects on glottal opening and closing function and phonation“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE -*www.icmje.org*) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o.) und werden von mir verantwortet.

Meine Anteile an den ausgewählten Publikationen entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o.) und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

_____

Datum Unterschrift

Anteilserklärung an den erfolgten Publikationen

Ahmed Ibrahim Nasr hatte folgenden Anteil an den eingereichten Publikationen:

Publikation 1: Nawka T, Sittel C, Arens C, Lang-Roth R, Wittekindt C, Hagen R, Mueller AH, **Nasr AI**, Guntinas-Lichius O, Friedrich G, Gugatschka M. Voice and respiratory outcomes after permanent transoral surgery of bilateral vocal fold paralysis. Laryngoscope 2015;125(12):2749-2755.

Beitrag im Einzelnen: Patientenrekrutierung und -betreuung im Studienverlauf, Durchführung von Literaturrecherchen, Beteiligung an der Durchführung der Untersuchungen.

Publikation 2: Caffier PP, **I Nasr A**, Weikert S, Rummich J, Gross M, Nawka T. The use of injectable calcium hydroxylapatite in the surgically pretreated larynx with glottal insufficiency. Laryngoscope 2017;127(5):1125-1130.

Beitrag im Einzelnen: Patientenrekrutierung und -betreuung im Studienverlauf, Durchführung von Literaturrecherchen, Beteiligung an der Durchführung der Untersuchungen; Mitarbeit bei der Erstellung des Manuskripts.

Publikation 3: Caffier PP*, **Ibrahim Nasr A***, Ropero Rendon MDM, Wienhausen S, Forbes E, Seidner W, Nawka T. Common Vocal Effects and Partial Glottal Vibration in Professional Nonclassical Singers. J Voice 2018;32(3):340-346. [* geteilte Erstautorenschaft]

Beitrag im Einzelnen: Patientenrekrutierung und -betreuung im Studienverlauf, Durchführung von Literaturrecherchen (Datenbanken Medline, Embase, Cochrane Library, Web of Science, SocIndex, PsyIndex, Psychinfo), Datenakquisation (auditiv-perzeptive Stimmbeurteilung, Videolaryngostroboskopie, DiVAS-Stimmfunktionsdiagnostik), Mitwirkung an der Auswertung der Primärdaten (LTAS-Spektren, Analyse partieller Vibrationen), Erstellung der Systematisierung nicht-klassischer Stimmeffekte und sämtlicher Abbildungen (Fig. 1, 2, 3, 4), Hauptanteil (neben Caffier PP, geteilte Erstautorenschaft) bei der Verfassung des Manuskripts.

_____

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers

_____

Unterschrift des Doktoranden

Publikation 1

Nawka T, Sittel C, Arens C, Lang-Roth R, Wittekindt C, Hagen R, Mueller AH, **Nasr AI**, Guntinas-Lichius O, Friedrich G, Gugatschka M. Voice and respiratory outcomes after permanent transoral surgery of bilateral vocal fold paralysis. Laryngoscope 2015;125(12):2749-2755. doi: 10.1002/lary.25415. Epub 2015 Aug 1.
https://doi.org/10.1002/lary.25415

Publikation 2

Caffier PP, **I Nasr A**, Weikert S, Rummich J, Gross M, Nawka T. The use of injectable calcium hydroxylapatite in the surgically pretreated larynx with glottal insufficiency. Laryngoscope 2017;127(5):1125-1130.
doi: 10.1002/lary.26261. Epub 2016 Aug
https://doi.org/10.1002/lary.26261

Publikation 3

Caffier PP*, **Ibrahim Nasr A***, Ropero Rendon MDM, Wienhausen S, Forbes E, Seidner W, Nawka T. Common Vocal Effects and Partial Glottal Vibration in Professional Nonclassical Singers. J Voice 2018;32(3):340-346. [* geteilte Erstautorenschaft]
doi: 10.1016/j.jvoice.2017.06.009. Epub 2017 Jul 12
https://doi.org/10.1016/j.jvoice.2017.06.009

Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht

Publikationsliste

Caffier PP, Nawka T, **Ibrahim Nasr A**, Thomas B, Müller H, Ko S-R, Song W, Gross M, Weikert S. Development of three-dimensional laryngostroboscopy for office-based laryngeal diagnostics and phonosurgical therapy. Laryngoscope 2018; 128(12):2823-2831. doi: 10.1002/lary.27260.

Caffier PP*, **Ibrahim Nasr A***, Ropero Rendon MDM, Wienhausen S, Forbes E, Seidner W, Nawka T. Common Vocal Effects and Partial Glottal Vibration in Professional Nonclassical Singers. J Voice 2018; 32(3):340-346. doi: 10.1016/j.jvoice.2017.06.009.
[* geteilte Erstautorenschaft]

Caffier PP, **I Nasr A**, Weikert S, Rummich J, Gross M, Nawka T. The use of injectable calcium hydroxylapatite in the surgically pretreated larynx with glottal insufficiency. Laryngoscope 2017; 127(5):1125-1130. doi: 10.1002/lary.26261.

Nawka T, Sittel C, Arens C, Lang-Roth R, Wittekindt C, Hagen R, Mueller AH, **Nasr AI**, Guntinas-Lichius O, Friedrich G, Gugatschka M. Voice and respiratory outcomes after permanent transoral surgery of bilateral vocal fold paralysis. Laryngoscope 2015; 125(12):2749-55. doi: 10.1002/lary.25415.

Danksagung

An erster Stelle möchte ich meinem Doktorvater PD Dr. med. Philipp Caffier, Oberarzt der Klinik für Audiologie und Phoniatrie der Charité, danken. Er hat mich während meiner wissenschaftlichen Arbeit und der Erstellung dieser Dissertation geduldig begleitet, sich immer Zeit genommen, mich fortwährend motiviert, sowie fachlich und menschlich großartig unterstützt.

Danken möchte ich auch dem ganzen Team der Phoniatrie an der Charité – Universitätsmedizin Berlin für die angenehme Zusammenarbeit, darunter insbesondere Prof. Dr. med. Tadeus Nawka, Prof. Dr. med. Manfred Gross, sowie Herrn Julius Rummich.

Weiterhin möchte ich mich bei Prof. Dr. med. Andreas Müller, Chefarzt der Klinik für Hals-Nasen-Ohrenheilkunde des SRH Wald-Klinikums Gera bedanken, der mir mit seinem Vertrauen die Chance auf Fortführung meiner beruflichen Tätigkeit in Deutschland gab und mir in vielen Diskussionen eine große Hilfe war.

Meinen Eltern möchte ich dafür danken, dass sie mir meinen Traum erfüllt haben, Medizin zu studieren. Sie standen und stehen mir jederzeit unterstützend und liebevoll zur Seite, ebenso wie meine Geschwister.

Bedanken möchte ich mich außerdem bei meinen Wegbegleitern sowie all meinen Freunden. Durch ihre Ermutigung und ihren emotionalen Rückhalt habe ich das Selbstvertrauen gefunden, diese Arbeit in Deutschland anzugehen und zu Ende zu bringen.